CASE REPORTS

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Penicillin Resistant Cases of Subacute Bacterial Endocarditis Successfully Treated with Massive Dosage

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SUBACUTE bacterial endocarditis caused by Streptococcus viridens can be successfully treated with penicillin.[1] Strains of Streptococcus viridens, however, vary in their resistance to chemotherapeutic agents. A practical measure of the sensitivity of resistance to penicillin is determined by the concentration of penicillin necessary to inhibit the growth of the organism in vitro.

If the growth of a strain of Streptococcus viridens is inhibited in the presence of less than 0.1 unit of penicillin per milliliter of serum, that strain may be said to be "sensitive." [2] If a strain of Streptococcus viridens is not inhibited in a concentration of 0.1 unit of penicillin per milliliter of serum, such a strain may be said to be "non-sensitive."

The majority of patients with subacute bacterial endocarditis, in which Streptococcus viridens is the etiological agent, will yield strains that fall into the "sensitive" group. Penicillin therapy with dosages in the vicinity of 300,000 to 500,000 units per day given in divided intramuscular injections every three hours for a minimum period of eight weeks, has been shown by Bloomfield and co-workers [2] to be adequate for the successful treatment of a "sensitive" strain.

Inadequate dosage of penicillin early in the course of treatment has been shown by Spink and co-workers [4] and others [2] merely to increase the resistance of the strain and, in some instances, to convert a "sensitive" strain to a "non-sensitive" one.

The following is the report of a patient in whom this phenomenon of increasing resistance to penicillin is demonstrated. Later this patient was apparently cured by three million units of penicillin daily for a period of more than ten weeks. A total of 338,510,000 units of penicillin was given this patient during a period of 13 months. To our knowledge this is the largest total amount of penicillin ever administered to a patient with subacute bacterial endocarditis.

REPORT OF CASE

A 25-year-old white man entered the Los Angeles County General Hospital on November 20, 1944. He had been slightly dyspneic on moderate exertion for two months. On November 16 he developed anorexia, general malaise, and a fever of 102 degrees F. On the following day he had a chill, and his temperature rose to 103 degrees F. He noted dull aching pains in his ankles, knees and back. On November 18 and 19 he had a non-productive cough and complained of chest pain, which was independent of respiratory motion.

The patient had had acute rheumatic fever when he was 11 years old. This was characterized by migratory joint pains in both ankles and knees, with fever and generalized weakness. He had no known heart involvement until two months prior to admission, when a private physician had told him he had a "murmur" and advised lighter work. He had had frequent sore throats until his tonsils were removed one year prior to entry. There was no history of congestive heart failure.

Physical Examination: Revealed a well developed and well nourished young man, moderately ill, but in no acute distress. Head and neck were essentially negative. Blood pressure was 150/80 mm. mercury. The apex impulse of the heart was palpated in 5th interspace at the mid-clavicular line; rhythm was regular with a rate of 90. The P2 sound was greater than the A2. There was a Grade II blowing systolic murmur heard at the apex and transmitted to the axilla. A diastolic murmur was not heard. The lungs and abdomen normal. The spleen was not palpable. The skin was clear and there were no petechiae.

Laboratory Findings: The Wassermann was negative. Urinalysis was reported as normal. The value for hemoglobin was 14.1 gm.; erythrocytes numbered 4,250,000 and leukocytes 7,800, with a normal differential. The sedimentation rate was 2 mm. in one hour (Wintrobe). Agglutination tests for typhoid, paratyphoid, typhus, and brucella were negative. Three blood cultures were positive for Streptococcus viridens before treatment was begun. The electrocardiogram was normal except for tendency toward right axis deviation. X-ray showed lung fields to be clear and cardiac enlargement was not noted.

A diagnosis was made of Subacute Bacterial Endocarditis, Probable Mitral Valvulitis. No cardiac enlargement. Class II D.

THERAPEUTIC PROGRAM

Sulfonamides: By December 1, 1944, ten blood cultures had been drawn, the first three of which had already yielded Streptococcus viridens. Sulfadiazine, 4 gm. initially and 1 gm. every four hours was given by mouth. On December 14, 1944, sulfadiazine was discontinued for two reasons. First, the blood cultures remained positive. Second, the tests in vitro showed that the strain of Streptococcus viridens obtained on blood culture was not inhibited in the presence of 20 mg. per cent of sulfanilamide, sulfathiazole or sulfadiazine. At a later date sulfamerazine was available and this was given orally for 30 days without benefit. No sulfonamide complications were manifest.

Artificial fever: Employing a standard variety of fever cabinet, two series of fever treatments were administered. Each series consisted of six fevers with a total of 29 hours above 104 degrees F. During each series a total of 6 gm. of sulfamerazine orally and 260,000 units of penicillin in divided intramuscular injections was administered. These treatments were ineffectual.

Penicillin: Penicillin was a drug of limited availability for civilian purposes in 1944. On December 7, 1944, penicillin was started, using 20,000 units intramuscularly every four hours. Two days later the dosage was diminished to 15,000 units every four hours. After a little more than three

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weeks of therapy, the dosage was further reduced to 10,000 units every four hours intramuscularly.

The blood cultures became negative during the first two weeks of treatment, but were positive soon after the dosage was reduced to 10,000 units every four hours. When it was realized that the dosage was inadequate, the schedule was increased on January 8, 1945, to 20,000 units every four hours. This was the maximum amount available for this patient at that time. On January 11, 1945, it was possible to increase this to 20,000 units every three hours. Despite this increase the blood cultures remained positive. With the increasing availability of penicillin the dosage was again increased on February 14 to 30,000 units every three hours. On March 28, this same dosage was given every two hours. The daily dose totaled 360,000 units. Blood cultures remained positive for Streptococcus viridens. On April 10, the dosage was increased to 40,000 units every two hours. Between May 3 and May 11, it was decided to administer 500,000 units daily by a continuous intravenous drip. This method was abandoned at the end of this period because of an extensive thrombophlebitis that developed in all extremities employed. Heparin was not used. On May 11, the previous schedule of 40,000 units every two hours intramuscularly was resumed and continued without interruption until October 25, 1945. During this period the blood cultures remained positive.

After discussion of the case history with Bloomfield,[3] a daily dosage of three million units was given by continuous intramuscular drip. Blood cultures drawn on the following day were sterile. Over a period of 14 months during which the patient was followed after penicillin therapy was discontinued on January 6, 1946, all blood cultures remained sterile.

Numerous blood samples were examined during the period from October 28 until November 4, 1945, to determine the concentration of penicillin in vivo at different times of the 24-hour period of continuous therapy. At no time was there a concentration under 0.5 units per ml.; the levels ranged from 0.5 U/ml. to 2.0 U/ml.

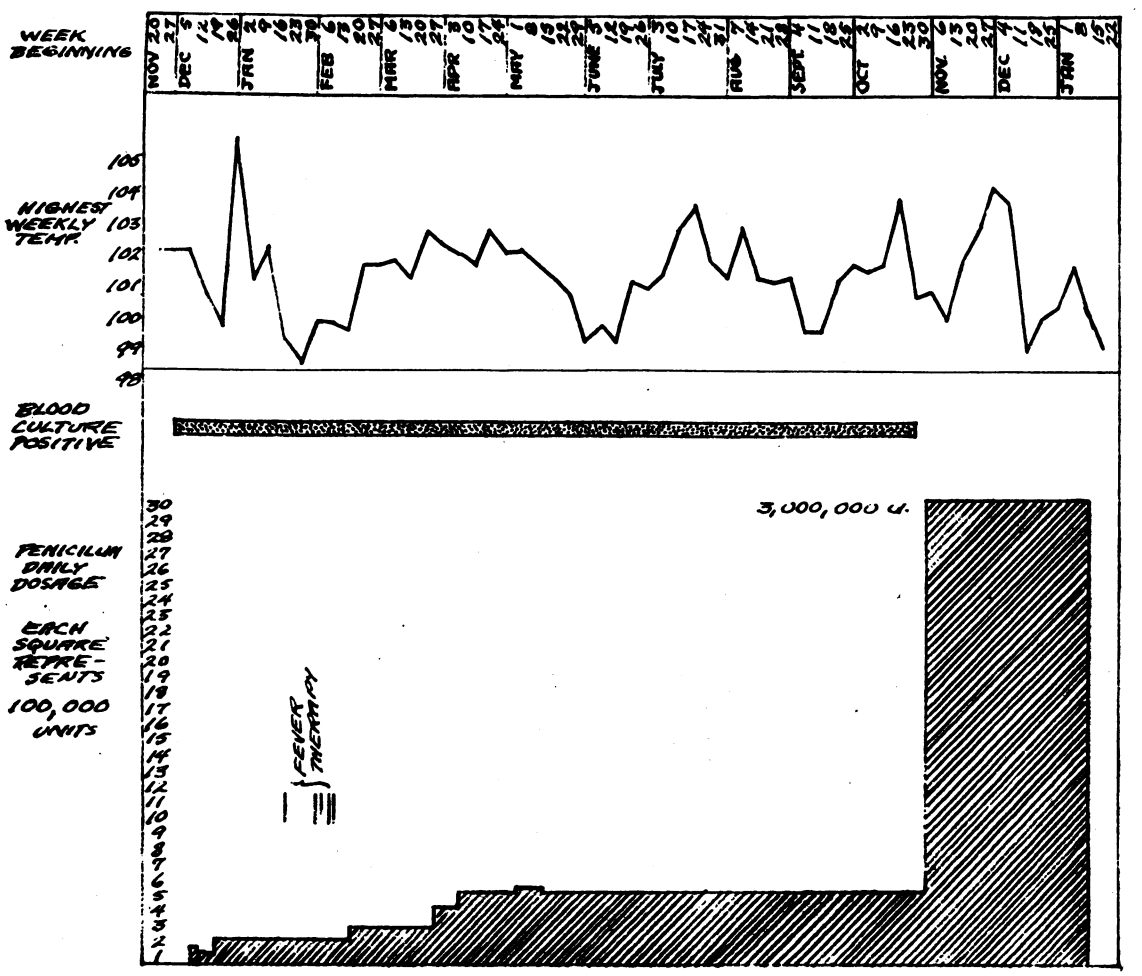
Sensitivity tests were reported as follows: On December 5, 1944, it required 0.2 unit per ml. to inhibit the growth of the streptococcus obtained on culture. On January 9, 1945, it required only 0.025 units per ml. to inhibit growth. After the reduction of penicillin dosage, the resistance of the organism to penicillin increased and the following units per ml. were required to inhibit growth: April 10, 1945, 12.5 units; May 11, 1945, 1.5 units; June 19, 1945, 50 units; July 21, 1945, 0.9 units; and September 7, 1945, 0.4 units. The organism at all times must be classed as "resistant" to penicillin. The resistance, however, increased during inadequate therapy. The wide variations of this test are not explained.

CLINICAL COMPLICATIONS

Anemia developed shortly after admission to the hospital, necessitating frequent blood transfusions.

A persistent fever was present (except for a few days

Chart 1.—Penicillin dosage, blood cultures, and highest weekly temperatures.



from the date of entry November 20, 1944) until three days after penicillin was discontinued on January 6, 1946. Since January 9, 1946, the patient has remained totally afebrile.

Auricular fibrillation developed once four weeks after the patient's entry into the hospital. A normal sinus rhythm was restored after three days of the administration of Cedilanid and small doses of quinidine.

Epistaxis was the most common hemorrhagic phenomenon in this patient. On one occasion the bleeding was so profuse that transfusion with whole blood became necessary. Small retinal hemorrhages were noted frequently. These were associated with transient episodes of blurred vision.

Petechiae were present on many occasions. They appeared in the retinae, conjunctivae and on the extremities.

A probable cerebral embolus with auditory aphasia developed on August 23, 1945. The significant positive findings which supported this diagnosis were (1) an inability to speak, (2) bilateral Babinski signs and hyperactive deep tendon reflexes. The patient was critically ill during this period. Nearly one month was required for the aphasia to clear significantly. Almost one year later the patient still had slight residual aphasia.

Renal colic was present on three distinct occasions. This was accompanied by the presence of red blood cells, white blood cells and a trace of albumin in the urine, which suggested an embolic glomerulo-nephritis, or small renal infarcts.

Thrombophlebitis developed in all veins employed for the continuous intravenous infusion of penicillin.

A sterile abscess developed in the thigh on December 2, 1945, after more than a month of continuous intramuscular drip of three million units of penicillin daily which was administered in 1 liter of normal saline. This abscess was incised and drained. Thick, brown, sterile pus was evacuated. Later both thighs became continuously inflamed until the penicillin was discontinued. The inflammatory process promptly subsided with the discontinuance of the penicillin, and three days after the drug was stopped, the temperature returned to normal levels for the first time in approximately 14 months of treatment.

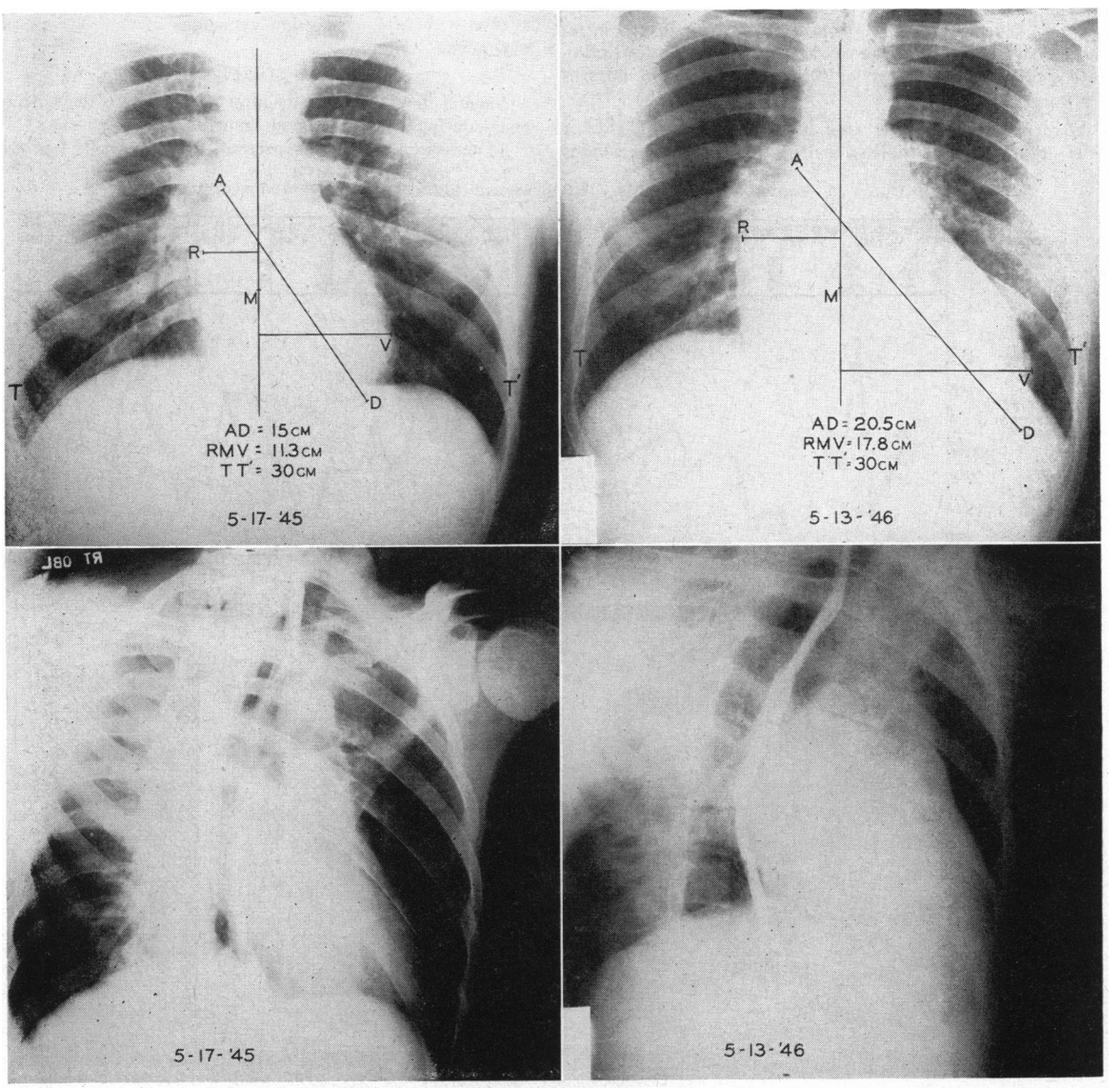


Figure 1.—Films of chest demonstrating cardiac enlargement occurring during treatment. The oblique views show the enlargement of the left auricle with posterior deviation of the esophagus.

Progressive heart disease during and following penicillin therapy was evidenced by increasing cardiac size (Figure 1). As late as May 17, 1945, fluoroscopic examination and films of the heart showed no evidence of cardiac enlargement. On May 13, 1946, less than a year later, the transverse diameter of the heart had increased from 11.3 cm. to 17.8 cm. The cardiothoracic ratio increased from 0.38 to 0.59. The longitudinal diameter of the heart increased from 15 cm. to 20.5 cm. In the right oblique position x-rays indicate the development of a marked posterior deviation of the esophagus which indicates left auricular enlargement.

Electrocardiograms taken before and after treatment show a change from a normal electrocardiogram to one in which there are large notched P waves, right axis deviation, and inverted T waves in leads II and III.

There was a definite change in the character of the heart findings. On the original examination the systolic murmur at the apex was a blowing murmur intensity grade II, and the blood pressure was 150/80. On re-examination on May 10, 1946, the intensity of the systolic murmur at the apex was graded as IV to V. It extended throughout the whole systole and ended with an unusually loud second sound which is unusual at the apex. No diastolic murmurs were heard. The blood pressure on May 10 was 148/106, and the diastolic pressure was consistently over 100 while the systolic pressure rose as high as 168.

Signs of congestive heart failure were thought to be present at the time of the patient's visit to the outpatient clinic in April, 1946, and he was admitted to the General Hospital for a period of ten days. At this time digitalis and ammonium chloride were given. Following this the shortness of breath and swelling of the ankles markedly improved, and the patient continued on the same program. He has returned to work.

CONCLUSIONS

1. A total of 338,510,000 units of penicillin was administered to a patient who had subacute bacterial endocarditis.

2. This patient who had a penicillin resistant strain of Streptococcus viridens and who was not benefited by 480,000 units of penicillin daily for six and one-half months, was apparently cured by three million units of penicillin daily for 72 days.

3. The patient's temperature remained elevated until three days after penicillin was discontinued, although the blood cultures were consistently negative immediately after beginning the three million unit daily dosage.

4. It is important to evaluate the penicillin sensitivity of the strain of Streptococcus viridens in order to properly treat subacute bacterial endocarditis. Extremely large doses of penicillin should be used early in patients who have a penicillin resistant strains of Streptococcus.

5. The dangers of inadequate early therapy are illustrated by relapse, by increased resistance to penicillin and by the rapid progression of the cardiac disease as evidenced by enlargement of the heart and congestive failure.

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Streptomycin Treatment of Tuberculous Tracheo-Bronchitis

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TUBERCULOUS tracheo-bronchitis has become recognized, during the past decade, as a frequent complication of pulmonary tuberculosis, which interferes with respiratory function, leads to spread of the disease, and often precludes the application of collapse measures otherwise indicated. Although many cases heal by resolution or by scarring which may lead to fibrous stenosis with further complications, the usual course is slow and hazardous. Accordingly a new treatment which has led to rapid healing of such lesions in every one of a series of cases so far treated appears worthy of report.

A white male, 26 years of age, found to have moderately advanced pulmonary tuberculosis on a routine x-ray examination, was admitted to a Veterans Administration hospital. Artificial pneumothorax was induced on the left side in July, 1946, and had been maintained since. Bronchoscopic examination in August, 1946, and again in September, 1946, showed ulceration and granulations in the left main stem bronchus more than half occluding its lumen. Streptomycin treatment was begun on September 5, 1946, the day after the second bronchoscopy, and was continued for a period of three months. Two grams of streptomycin was given in six intramuscular injections, four hours apart, every day, and 0.5 gm. of streptomycin was given daily by aerosol inhalation every two hours during the daytime.

Repeated bronchoscopic examination showed remarkably rapid subsidence of the lesion, with disappearance of the obstructing granulations and restoration of apparently normal mucous membrane in an only slightly narrowed bronchus in only six weeks. Repeated bronchoscopic examinations in the six months since cessation of the treatment have shown no evidence of recurrence. The patient's sputum has become negative and there has been marked clinical improvement, both physically and psychically, although rest and the pneumothorax regimen are being continued. During the second month of treatment the patient was considerably disturbed by symptoms of vestibular dysfunction, and since then has shown a complete absence of response to caloric tests. He has adjusted well, however, and shows good compensation by the use of other senses.

Twenty other patients, treated with streptomycin for periods of from one week to three months have all shown the same rapid healing of open ulcerative or granulating tuberculous lesions of the trachea and bronchi. Recently much smaller doses without aerosol have yielded similar success with no vestibular dysfunction.

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Latent Malaria

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RECENTLY there have been frequent warnings of the need for physicians to be more aware of those diseases not commonly seen in temperate climates but likely to be prevalent now by virtue of the return of those in the armed forces who have served overseas. No one will deny that malaria must be included in this group. London and others,[1] in a study of the delayed primary attack of vivax malaria, found in 101 cases a variation of onset of 3 to 104 (mean 41) days after cessation of suppressive medication. Most and Hayman[2] have described uncommon clinical variations in malaria and stated that the delayed primary attack may occur in a few individuals as long as a year after the cessation of